

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

**PCT**

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

### FOR FURTHER ACTION

See paragraph 2 below

International application No. PCT/US2008/012149	International filing date (day/month/year) 24.10.2008	Priority date (day/month/year) 26.10.2007
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International Patent Classification (IPC) or both national classification and IPC  
INV. C07D233/86 A61P35/00 A61K31/4166

Applicant  
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

#### 1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

#### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

#### 3. For further details, see notes to Form PCT/ISA/220.

*Written Opinion*

2 MONTH REMINDER 5/29/09

1 MONTH REMINDER 6/29/09

2 WEEK REMINDER 7/15/09

3 DAY REMINDER 7/26/09

ACTION DUE AND DATE 7/29/09

Name and mailing address of the ISA:



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Date of completion of  
this opinion

see form  
PCT/ISA/210

Authorized Officer

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:  
 the international application in the language in which it was filed  
 a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2.  This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:  
 a sequence listing  
 table(s) related to the sequence listing
  - b. format of material:  
 on paper  
 in electronic form
  - c. time of filing/furnishing:  
 contained in the international application as filed.  
 filed together with the international application in electronic form.  
 furnished subsequently to this Authority for the purposes of search.
4.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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**Box No. II Priority**

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1.  The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2.  This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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**Box No. IV Lack of unity of invention**

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1.  In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
  - paid additional fees
  - paid additional fees under protest and, where applicable, the protest fee
  - paid additional fees under protest but the applicable protest fee was not paid
  - not paid additional fees
2.  This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
  - complied with
  - not complied with for the following reasons:

**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
  - all parts.
  - the parts relating to claims Nos. 1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part)

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	<u>1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part)</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part)</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part)</u>
	No: Claims	

2. Citations and explanations

**see separate sheet**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2008/012149

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)  
and / or
2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 **Reference** is made to the following documents:

D1: WO 2006/124118 A (UNIV CALIFORNIA [US]; SAWYERS CHARLES L [US]; JUNG MICHAEL E [US]; CHE) 23 November 2006 (2006-11-23).

**Re Item IV.**

2 This International Searching Authority found multiple groups of inventions in this international application, as follows:

**Invention 1:** Claims 1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part) are directed to: 1[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(4-substituted propyl-phenyl)-5-oxo-2-thioxo-imidazolidine derivatives, with **R3 being hydrogen** in the general formula of claim 1, pharmaceutical compositions and the medical use of such compounds for the treatment of proliferative diseases such as cancer.

**Invention 2:** Claims 1-8 (in part), 11-13 (in part), 14-15, 20-21, 22-32 (in part), 34-39 (in part) are directed to: 1[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(4-substituted propyl-phenyl)-5-oxo-2-thioxo-imidazolidine derivatives, with **R3 being cyano** in the general formula of claim 1, pharmaceutical compositions and the medical use of such compounds for the treatment of proliferative diseases such as cancer.

**Invention 3:** Claims 1-8 (in part), 11-13 (in part), 18, 22-32 (in part), 34-39 (in part) are directed to: 1-[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(4-substituted propyl-phenyl)-5-oxo-2-thioxo-imidazolidine derivatives, with **R3 being formyl** in the general formula of claim 1, pharmaceutical compositions and the medical use of such compounds for the treatment of proliferative diseases such as cancer.

**Invention 4:** Claims 1-8 (in part), 9 (in part), 11-13 (in part), 16, 19, 22-39 (in part) are directed to: 1-[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(4-substituted propyl-phenyl)-5-oxo-2-thioxo-imidazolidine derivatives, with **R3 being**

**carbonyl-R13** in the general formula of claim 1, a process to make these compounds, pharmaceutical compositions and the medical use of such compounds for the treatment of proliferative diseases such as cancer.

**Invention 5:** Claims 1-7 (in part), 10, 11-13 (in part), 17, 22-39 (in part) are directed to: 1-[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(4-substituted propyl-phenyl)-5-oxo-2-thioxo-imidazolidine derivatives, with **R3 being Imidazol-2-yl or Imidazolin-2-yl** in the general formula of claim 1, a process to make these compounds and pharmaceutical compositions and the medical use of such compounds for the treatment of proliferative diseases such as cancer.

**Invention 6:** Claims 1-7 (in part), 9 (in part), 11-13 (in part), 16 (in part), 22-32 (in part), 34-39 (in part) are directed to: 1-[(4-Cyano-3-trifluoromethyl-phenyl)]- 3-(4-substituted propyl-phenyl)-5-oxo-2-thioxo-imidazolidine derivatives, with **R3 being Methylamidinyl** in the general formula of claim 1, pharmaceutical compositions and the medical use of such compounds for the treatment of proliferative diseases such as cancer.

- 2.1 The inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:
- 2.2 According to Rule 13.1 PCT, "The international application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".
- 2.3 This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features that defines a contribution which each of the inventions, considered as a whole, makes over the prior art".
- 2.4 *A priori*, the only technical relationship being able to unite the different inventions is the special technical feature represented by the Markush formula of claim 1 and the therapeutic effect compounds described by said formula have on proliferative

diseases like cancer.

- 2.5 To decide whether these technical features are special technical features, the teaching of Rules 13.1 and 13.2 PCT must be applied, which stipulate that the technical feature must define a contribution over the prior art to be recognized as the special technical feature, which then would give rise to unity.
- 2.6 The prior art document D1 discloses: 1[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(4-substituted propyl-phenyl)-5-oxo-2-thioxo-imidazolidine derivatives falling into the scope of the general formula of claim 1 (see D1, example RD130/page 56, RD131/page 57, RD169/page 83 and claim 18, RD170/page 85 and claim 19), pharmaceutical compositions (see D1, claim 20) and the medical use of such compounds for the treatment of proliferative diseases such as cancer (see D1, claim 23 and 31). D1 therefore discloses already said technical features
- 2.7 Effectively, the prior art document D1 destroys the novelty of claim 1 and the Markush formula of claim 1 does not constitute a special technical feature.
- 2.8 Thus, with the *a priori* formulated common concept uniting the above listed inventions already being known, the requisite unity of invention (Rule 13.1 PCT) therefore does not exist since a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT is not present.
- 2.9 The application, *a posteriori* does not meet the requirements of unity of invention as defined above.
- 2.10 In the light of the above, the examiner has, *a posteriori*, identified six different inventions. Considering the grouping of the inventions, due account has been taken of the search work involved, the grouping follows the order as suggested by the claims as originally filed, and in line with Article 17(3)(a) the first invention mentioned was chosen (R3=H).
- 2.11 Since the applicant has not paid further fees, the subsequent statement on novelty and inventive step will only relate to the first invention.

**Re Item V.**

Reasoned statement with regard to novelty and inventive step.

Claims 23-32 relates to subject-matter considered by this authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions, for use in a first or further medical treatment.

**3 Novelty**

3.1 The subject-matter of claims 1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part) **is new** in the sense of Article 33(2) PCT.

3.1.1 The prior art document D1 as the closest prior art discloses: 1[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(**4-substituted propyl-phenyl**)-5-oxo-2-thioxo-imidazolidine derivatives, pharmaceutical compositions (see D1, claim 20) and the medical use of such compounds for the treatment of proliferative diseases such as cancer (see D1, claim 23 and 31).

3.1.2 The difference between the prior art document D1 and the present application is: D1 does not disclose compounds, where the substituent in 3-position of the propyl group on the **4-propyl-phenyl** group is hydrogen. Thus, D1 does not disclose compounds, where the variable R3 (using the applicants nomenclature of claim 1) represents hydrogen. Instead, D1 discloses compounds, where R3 represents Methoxycarbonyl (see D1, RD129/page 55), Hydroxycarbonyl (42c, page 56), Aminocarbonyl (RD130/page 56, RD131/page 57, RD169/page 104), Methylsulfonylaminocarbonyl (RD157/page 57), Anilinocarbonyl (RD142/page 77), Cyano (RD170/page 85), and Azido (RD2/page 108)

3.1.3 Due to this difference, the subject matter of the claims 1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part) is novel.

#### 4 Inventive Step

4.1 The present application **does not meet** the criteria of Article 33(1) PCT, because the subject-matter of claims 1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part) **does not involve an inventive step** in the sense of Article 33(3) PCT.

4.1.1 Document D1 represents the closest prior art. D1 discloses: 1[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(**4-substituted propyl-phenyl**)-5-oxo-2-thioxo-imidazolidine derivatives, the formula of which is described by claims 1 (see D1, page 121), pharmaceutical compositions (see D1, claim 20) and the medical use of such compounds for the treatment of proliferative diseases such as cancer (see D1, claim 23 and 31).

4.1.1.1 It is noted in this context, that D1 and the present application are addressing the same problem.

4.1.2 The compounds of the first invention, claims 1 (in part), 4-7 (in part), 11-13 (in part), are described by the general formula in claim 1 of D1. D1 states, that the 4-substituent on the 3-phenyl group in 1-[(4-Cyano-3-trifluoromethyl-phenyl)]-3-(substituted **phenyl**)-5-oxo-2-thioxo-imidazolidines can be "C1-C6 alkyl, optionally substituted". Thus, "R3" (variable used in claim 1 of present application) representing "hydrogen" (first invention) is described in D1.

4.1.3 The present application (invention 1) is thus a selection from D1.

4.1.4 No technical effect for this selection is reported.

4.1.5 In the absence of comparative data, the objective technical problem thus becomes the provision of alternative 5-oxo-2-thioxo-imidazolidines with anti-proliferative activity.

4.1.6 A person skilled in the art, knowing about D1, can arrive at the claimed subject matter without any inventive step. The skilled person will use the teaching from D1 to arrive at the subject matter of the invention. Thus, the subject matter of the present application (invention 1) is obvious.

4.2 The subject matter of claims 1 (in part), 4-7 (in part), 11-13 (in part), 22-32 (in part), 34-39 (in part) is therefore not inventive.

**Re Item VIII.**

Certain observations on the international application

5 The application does not meet the requirements of Article 6 PCT, because claims 1 (in part), 4-7 (in part), 11-13 (in part), 34-35 (in part) and 37-38 (in part) are not clear:

5.1 Claims 1 (in part), 4-7 (in part), 11-13 (in part) are not clear, because the description casts doubt on the scope of the claims by defining the value "cycloalkyl" and "aryl" in the description in a way deviating from the universally accepted meaning of these terms as defined by IUPAC.

5.1.1 In the description page 8, paragraph [0020], the term "cycloalkyl" comprises, according to the applicant, also "partially unsaturated cyclic hydrocarbons", "polycycles" and "rings which may be fused with 1 or 2 aromatic rings". This is contrary to IUPAC Rule A 11-1, which states that cycloalkyl is "the name of **saturated monocyclic** hydrocarbons".

5.1.2 In the description page 10, paragraph [0027], the term "aryl" is said to "optionally include...heterocyclic rings (such as heteroaryl or cycloheteroaryl)". This is contrary to IUPAC rule A 13.1, which states that "aryl" stand for "radicals derived from monocyclic substituted aromatic hydrocarbons". Thus, "aryl" is not including "heteroaryl" or "cycloheteroaryl".

5.2 Claims 23 to 32 refer to a method of treatment, which, according to this

authority relates to subject-matter covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. Reference is made to the introductory passage in Item V.

- 5.3 Claim 34 is not allowable, as it defines its scope by a result to be achieved (See PCT GL II, 5.35).
- 5.4 Claim 35 is not clear, as the scope is defined by unclear and relative terms such as "above a first predetermined level" and "below a second predetermined level".
- 5.5 Claims 37 and 38 are not clear, as the term "AR" in "AR response reporter system" is not unambiguous.
- 5.6 Claim 38 furthermore is not clear, as the clause "..stimulation comprises measuring fold induction" is not intelligible.

## Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

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General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	<p>In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT).</p> <p>If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).</p>
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003